

CHROMOSOME FUSION

I. THE CHALLENGE

A. OBSERVATIONS

1. Observe the human Chromosome #2 and the matching ape chromosomes (**Fig. 1**). The constriction (narrowing) just above the middle of our chromosome 2 (Hu) is called the **centromere**. The shorter segment of the chromosome (*above* the centromere constriction) is called the “p” arm; the longer portion (*below* the centromere) is called the “q” arm. Each arm is divided into numbered regions and sub-regions, and within each sub-region, the dark and light bands may be further identified by decimal numbers. The identification number (ID) for any particular band is a combination of these letters and numbers. For example, the lowest tip end band of chromosome #2 is: 2q37.3. Be sure to confirm that on **Fig. 1**.
2. Notice the identical banding patterns between the corresponding arms of the human (Hu) and the two chimpanzee (Ch) chromosomes. Our “p” arm is nearly identical to the chimp’s upper chromosome, and our “q” arm is nearly identical to the chimp’s lower chromosome.
3. Look carefully at the region near the middle of *our* chromosome 2 that corresponds to where the tip ends of the two matching chimp chromosomes overlap and where the bands are *not* identical to those in our chromosome 2. Do you see the white band located there, labeled **2q13**?

B. INTERESTING QUESTION: Why does our chromosome #2 appear to be so very similar to the two shorter chromosomes found in apes (chimpanzees, gorillas, and orangutans)?

C. SOME POSSIBLE EXPLANATIONS (Building a Working Hypothesis):

1. They were designed that way.
2. Chromosome 2 split into two (fission) in the ancestral branch (or branches) that produced the apes.
3. Chromosome 2 formed from the joining (fusion) of two shorter chromosomes in an early human ancestor after the apes branched off.

To suggest “design” as an explanation usually implies a supernatural designer, and since supernatural forces cannot be reliably tested or disproved (basic requirement for all scientific explanations), “design” cannot be properly considered as a scientific explanation.

Other studies (fossil and molecular) have suggested that the gorillas and orangutans apparently branched off (from an evolutionary line leading to humans) earlier than when the chimps branched off. So explanation #2 (above, identical fissions) would have been required to happen 3 times independently, and this is very unlikely.

That leaves explanation #3, namely that human chromosome #2 probably resulted from the head-to-head **fusion** (joining) of those two smaller chromosomes in an early human ancestor *after* the apes branched off. This is the hypothesis that we will be testing. We will want to look for evidence of that **ancestral fusion** in our current chromosome #2.

D. DNA DETAILS DETOUR: If you are unfamiliar with details of chromosome orientation, chromosome telomeres, telomere structure (and variations), 5’-3’ and 3’-5’ orientations of the parallel strands of a DNA molecule, and the only way two DNA molecules can join, study the DNA DETAILS beginning on page 3, then return to this point to continue.

E. PREDICTION: If fusion happened, there should be evidence of the two telomeres from the two ancestral chromosomes in that apparent fusion region (2q13) near the middle of our chromosome #2. If we can find the DNA sequences of two sets of head-to-head telomeres in the suspected fusion region, this would provide strong evidence that our chromosome #2 was indeed formed from the head-to-head fusion of two shorter chromosomes from our earlier ancestry (the same two chromosomes we find separately today in the apes). The existence of head-to-head telomeres mid-chromosome would otherwise be hard to explain. This evidence further strongly confirms a close kinship of humans and apes.

F. THE TEST: To test our selected hypothesis, you will need to **search** the suspected fusion region in chromosome 2 for evidence of head-to-head telomeres. If that evidence is found, our hypothesis is strengthened. If evidence is not found, the hypothesis may not be correct.

II. THE SEARCH

DO ONE OR MORE OF THE FOLLOWING SEARCHES

IF YOU HAVE INTERNET ACCESS: Do **Part A** (below) to get oriented to the region of interest in chromosome #2, and to get a working sense of the vast amount of DNA there, and how difficult it is to find a particular sequence. You shouldn't spend more than about 5 minutes searching. At that point, you should either go on to **Part B** to do the BLAST2 search, or (if assigned) do **Part D** to search the printed copy of DNA in the fusion region. If you have time (or for homework) do **Part C**, which will take you to a fascinating discovery.

IF YOU DO NOT HAVE INTERNET ACCESS: Do **Part D**. You will need to get copies of all the Figures, along with a copy of Part D directions.

PART A. VISUAL SEARCH ONLINE with NCBI

Uses the NCBI website, with its great visual maps showing locations from which the many cloned segments were taken, along with detailed DNA sequences arranged in rows (as used in this lesson): <http://www.ncbi.nlm.nih.gov/mapview/maps.cgi>.

PART B. SEARCH WITH the "BLAST2" SEARCH TOOL on NCBI

This is one of the online tools that scientists use to look for specific sequences. It involves entering a short search sequence "probe" and specifying the DNA region to search. <http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi>

PART C. SEARCH on the SANGER GENOME BROWSER

The Sanger Institute (Human Genome Browser: e! Ensembl Human), shows the linear arrangement of DNA, with each nucleotide in a different color, plus the complementary matching sequence, and all the possible amino acids coded for. Very colorful: http://www.ensembl.org/Homo_sapiens/index.html.

PART D. PAPER SEARCH on the ONE-PAGE COPY OF DNA in the FUSION REGION

If online access is not available, use the provided page showing the DNA sequence copied from the tiny portion of the 2q13 region where telomere fusion should be found.

GO TO THE PAGE WITH THE PART YOU WILL BE WORKING ON

DNA DETAILS

DNA STRUCTURE

1. As you probably remember from your earlier studies, DNA is a double-stranded ladder-shaped molecule (when it's untwisted from its normal helix shape). In addition, you should recall that each "rung" of the ladder consists of a "base-pair" of two nucleotide bases, with only the following pairings: t&a, a&t, g&c, or c&g. The sample below shows these pairings:

```
ttagggttagggttagggttagggttagggttagggttagggttaggg← Strand 1
|||||
aatcccaatcccaatcccaatcccaatcccaatcccaatccc← Strand 2
```

2. Since each letter in strand 2 can be inferred (and assumed) from its matching letter in strand 1, we often just work with one strand to keep it simpler and take less space, as shown below:

```
ttagggttagggttagggttagggttagggttagggttagggttaggg← Strand 1
```

However, each letter (base) in strand 1 may still be called a "base-pair" (bp), reflecting the fact that it *represents* a matched pair of bases at that position in the complete DNA molecule.

3. By the way, do you see the repeating pattern in that sequence? If not, try saying the letters in that sequence out loud. You should see that the sequence ttagggttaggg repeats over and over again. These are called "tandem repeats." In order to clarify this pattern, we can insert a break between each set (although, in reality, there are no breaks), so strand 1 would look like this:

```
ttagggttaggg ttagggttaggg ttagggttaggg ttagggttaggg ttagggttaggg ttagggttaggg
```

This particular series of tandem repeats (of these six bases, usually repeated 800 to 1600 times), is always found at both ends of every chromosome. These "end pieces" of DNA, called "**telomeres**," are like the ends of shoelaces, keeping the chromosome ends from "unraveling" or getting damaged.

4. In reality, these sequences may vary slightly, especially as the telomere region comes closer to the non-telomere DNA. For example, part of the sequence might look like this:

```
ttagggttaggg ttgggg ttagggttaggg ttgggg ttgggg ttgggg
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See the differences? In any case, the most characteristic feature of a telomere is its many, many repeats of 3-4 g's at a time, and virtually no c's in that strand. Take another look at the sample to confirm this.

DNA ORIENTATION

5. In order to understand what you will be seeing in the real DNA sequences while looking for evidence of fusion, you need to recognize how the two strands in DNA are oriented relative to each other, and how this orientation relates to our conventional orientation of chromosomes.

6. Chromosomes in a karyotype (total chromosome array for a species) are typically oriented with their *centromeres* above the midpoint of each chromosome (somewhere between the midpoint and the end of the shortest arm, which we call the "p" arm); see the **Introductory Figure**, showing the karyotypes of humans (properly oriented) and 3 ape species, side by side for each corresponding chromosome, oriented to show closest matching. The uppermost end of each human chromosome (with the shorter, or p, arm) is called the "head end."

7. The single DNA molecule in each chromosome is, of course, composed of two parallel strands, held together by the hydrogen bonds between its matching base pairs. Something you may or may not have learned is that one strand is oriented *upside down* relative to the other. The deoxyribose sugars in both strands are comprised of carbon atoms numbered from one to five. See **Figure 5**. When the number 5 carbon attaches to the phosphate group above it, and the number 3 carbon connects to the phosphate below it, we say that it is oriented 5' to 3' (5 prime to 3 prime). This is the orientation of strand 1. Its companion strand (strand 2), is oriented oppositely: 3' to 5'. The matching bases require this opposing orientation in order to bond properly to each other, holding the two strands together.

